REMARKS

By the present communication, no claims have been amended, canceled or added. Upon entry of the present amendment, claims 93, 101-105 and 108-130 are pending in this application.

Rejections under 35 U.S.C. §112, First Paragraph

Applicants respectfully traverse the rejection of claims 93, 105 and 108-130 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action alleges that SEQ ID NO:7 has not been shown to work in any other way than that of a carrier in combination with an antibiotic or GM-CSF to either treat infection or stimulate innate immunity, which antibiotics and GM-CSF are known to do alone, and that the evidence previously submitted via the declaration of Dr. Donini is inconclusive to show these effects of the peptide (page 5, lines 11-15 of the Office Action).

Evidence of the ability of SEQ ID NO:7 to act alone in treating infection or stimulating innate immunity is disclosed in Example 12 and corresponding Figure 1 of the specification which demonstrate the ability of SEQ ID NO:7 to inhibit systemic *S. aureus* infection. Applicants point out that in addition to showing administration of SEQ ID NO:7 in combination with an antibiotic, Figure 1 also shows administration of SEQ ID NO:7 alone and not in combination with antibiotic as evidenced in the second (2.5 mg/ml) and third (10 mg/ml) columns of the graph depicted in Figure 1. Such mice had bacterial blood counts of less than 10,000 CFU/ml while mice not treated with either peptide or antibiotic had bacterial blood counts of over 15,000 CFU/ml. Applicants respectfully submit that the specification clearly demonstrates SEQ ID NO:7 as having immune system stimulatory activity (efficacy against infection).

Additional evidence of the ability of SEQ ID NO:7 to act alone in treating infection or stimulating innate immunity is disclosed in Tables 50 and 51 of the specification, which show the effect of SEQ ID NO:7 alone on *Salmonella* and *S. aureus* infection, respectively. Table 50 shows bacterial counts in the spleens of mice infected with *Salmonella*. *Salmonella* infected

mice treated with SEQ ID NO:7 had bacterial counts of approximately 5.4 x 10^3 CFU/ml while mice not treated with SEQ ID NO:7 had bacterial counts significantly higher at approximately 1.88 x 10^4 CFU/ml. Table 51 shows bacterial counts in blood of mice infected with *S. aureus*. *S. aureus* infected mice treated with SEQ ID NO:7 had bacterial blood counts of approximately 3.8 x 10^3 CFU/ml while those not treated with SEQ ID NO:7 had bacterial counts significantly higher (almost double) at approximately 7.6 x 10^3 CFU/ml.

As additional support to show the ability of SEQ ID NO:7 to treat infection or stimulate innate immunity, Applicants submit herewith the declaration of Dr. Oreola Donini, Senior Director of Preclinical Research and Development at Inimex Pharmaceuticals, Inc. Included in the declaration are the following exhibits: 1) a report written by Dr. Donini presenting experimental data showing the efficacy of SEQ ID NO:7 in various infection model studies (Exhibit A); 2) a report written by Dr. Donini presenting experimental data showing the efficacy of SEQ ID NO:7 in various infection model studies which was submitted as Exhibit B to the declaration submitted with the previously filed response of October 4, 2007 (Exhibit B); and 3) the curriculum vitae of Dr. Donini (Exhibit C). Specifically, both reports (Exhibits A and B) describe various infection models using SEQ ID NO:7 alone, demonstrating immune system stimulatory activity (efficacy against infection), anti-inflammatory activity, and anti-sepsis activity.

With regard to treating infection or stimulating innate immunity using only SEQ ID NO:7, Dr. Donini presents evidence demonstrating the *in vivo* efficacy of SEQ ID NO:7 in a number of intra-peritoneal (IP) infection models, including multiple pathogens, routes of administration and dosing regimes. As discussed in the declaration, Figures 1, 2, 4-9 and 10a of Exhibit A all show dramatic reductions in bacterial counts associated with administration of SEQ ID NO:7 *alone* in intra-peritoneal (IP) infection models.

Applicants point out that as shown in Table 54 of the specification, SEQ ID NO:7 has no significant antimicrobial activity. Accordingly, the ability of SEQ ID NO:7 to prevent or reduce bacterial infection is due to its ability to stimulate innate immune system and treat infection.

This is exemplified in the experiment presented on pages 7 and 8 of Exhibit A entitled 'Independent of Adaptive Immune System', and related Figures 7a and 7b which show that the action of SEQ ID NO:7 is through stimulation of the innate immune system, and independent from the adaptive immune system. For example, the experimental data shows reduction of *S. aureus* infection in RAG1 mice which lack both T and B cells, major components of the adaptive immune system (see Figures 7a and 7b). Accordingly, the data shows that stimulation of the innate immune system by SEQ ID NO:7 does not rely on the presence of effector cells of the adaptive immune system. Additionally, due to the clearly shown ability of SEQ ID NO:7 to reduce bacterial infection, SEQ ID NO:7 reduces the probability that an infection will proceed to systemic inflammation (i.e., sepsis) and therefore additionally exhibits anti-sepsis activity.

With regard to anti-inflammatory and anti-sepsis activity, Dr. Donini presents additional evidence of *in vivo* infection models demonstrating that SEQ ID NO:7 is capable of such activity. The results shown in Figures 3 and 10b of Exhibit A of the declaration clearly indicate that in addition to aiding in the resolution of infection, SEQ ID NO:7 is simultaneously able to modulate inflammation by substantially reducing the inflammatory cytokine response to infection (i.e., TNF-α levels, a key instigator of inflammation) thus reducing the probability of infection progressing to systemic inflammation (i.e., sepsis).

As indicated on page 5 of Exhibit A, a dramatic reduction in proinflammatory cytokine TNF-α levels in an intraperitoneal (IP) *S. aureus* model is evidenced. The infection model included IP injection of mice with *S. aureus* and subsequent injection with SEQ ID NO:7 four hours later. As shown in Figure 3, TNF-α levels present in the peritoneal fluid were then assessed showing a dramatic reduction as compared to untreated mice. Similarly, as indicated on page 10 of Exhibit A, a dramatic reduction in TNF-α levels in a murine pneumonia model is evidenced. The pneumonia model included intranasal delivery of *S. pneumonia* and IP injection of SEQ ID NO:7 at the time of infection or 24 hours subsequent to the time of infection. As shown in Figure 10b, TNF-α levels present in the broncheoalveolar lavage (BAL) fluid were then

assessed, showing a dramatic reduction as compared to untreated mice and mice treated with the antibiotic azithromycin.

Additional experimental data, originally submitted in Exhibit B to the declaration submitted with the previously filed Response of October 4, 2007, and resubmitted herewith as Exhibit B of the current declaration, provides additional evidence of the anti-inflammatory activity of SEQ ID NO:7. For example, as shown on page 5 of Exhibit B, a dramatic reduction in proinflammatory cytokine TNF-α and IL-6 levels in an intraperitoneal (IP) *S. aureus* model is evidenced. The infection model included IP injection of mice with *S. aureus* and IP injection of SEQ ID NO:7 four hours before the time of infection or 24 hours subsequent to the time of infection. As shown in Figure 8 of Exhibit B, TNF-α and IL-6 levels present in the peritoneal fluid were then assessed showing a dramatic reduction as compared to untreated mice. Similarly, as indicated on page 5 of Exhibit B, a reduction in inflammation is evidenced in a murine model. The model included induction of ear inflammation in CD-1 mice using phorbol myristate acetate (PMA) and topical administration of SEQ ID NO:7 30 minutes before and 30 minutes after induction. Ear weight was then assessed 6 hours after inflammation was induced. As shown in Figure 9 of Exhibit B, the average weight of SEQ ID NO:7 treated ears was found to be over .01 grams (greater than 15%) less than untreated ears.

As additional evidence, Applicants respectfully submit that the specification clearly teaches the anti-inflammatory activity of SEQ ID NO:7. For example, Table 4 of the specification discloses the reduction of *E. coli* lipopolysaccharide (LPS) induced TNF-α production in mouse macrophage cells by SEQ ID NO:7. Macrophage cells treated with SEQ ID NO:7 were shown to have approximately 50.5% decreased TNF-α production as compared to untreated cells. Additionally, the role of TNF-α as a pro-inflammatory cytokine and its link to initiating inflammation, is described in the specification in paragraph [0007], as well as being known to one skilled in the immunological arts. Paragraph [0007] discloses the following:

> The presence of microbial components induce the release of pro-inflammatory cytokines of which tumor necrosis factor-α (TNF-α) is of extreme importance. TNF-α and other

pro-inflammatory cytokines can then cause the release of other pro-inflammatory mediators and lead to an inflammatory cascade.

In light of the foregoing reasons and declaration submitted herewith providing substantial experimental data showing evidence of the anti-inflammatory, anti-sepsis, and immune system stimulatory activity of SEQ ID NO:7, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

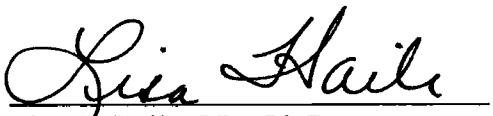
Conclusion

In view of the amendments and above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

The Commissioner is hereby authorized to charge $525.00 as payment for the Three-Month Extension of Time fee and any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: August 21, 2008



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